Magazine

False starts

Empty chateaux

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When I woke up on the morning of Tuesday 27th June 2000, I noticed no change at all. I telephoned a few friends and they confirmed that their lives were not much different that morning. One said he had a slight hangover but he could account for this minor deviation. For years we had been told that once we had the sequence of the human genome, everything would change. So how come after the rough draft of the sequence was announced in a grand ceremony at the White House, neither I nor my friends experienced any of the predicted effects. Was it the roughness of the draft, I wonder, or does the magic still lie concealed in the 5–15% of the genome that is either un-sequenced or unassembled?

Although there are many candidates contending for credit for the sequence, it seems that the Almighty got a fair share of it that Monday. One of the leaders of the Western world was quoted as saying that we had uncovered the script that God used to create human life, thus reducing the human achievement to a modest piece of celestial gene hacking. Some commentators stated that we had now "deciphered" the human code, an exaggeration that may well survive unbeaten this millennium. And, of course, there was a great deal of discussion on whether this was the beginning of the end, or the end of the beginning, or somewhere in the middle of the beginning of the beginning.

We know we are nowhere near the end because of the still great uncertainty in the number of genes in the human genome. Three recent papers, which got the popular press steamed up, each gave different estimates, ranging from about 25,000 to more than 120,000. People get quite shaken by these wild fluctuations and they really want to know whether they are only twice as complicated as a fly or as a worm, or whether they can seek comfort in the larger number. My bet is that it will be close to 50,000. I would prefer to call these genetic loci rather than genes; it will take some time to find out how many different functional products these loci have.

After every party some people always stay behind to clear up the mess and put everything away. The captains and the kings have departed, the shouting has died down and hyperventerlation has ceased. We can walk around the deserted chateau and look at the ancestral portraits on the wall. In Chateau Genome we would find evidence to refute the impression given by the press that the sequencing was carried out by two people starting from scratch, with a little bit of help from Jim Watson.

The first person to set up a large sequence project was Akiyoshi Wada, who, in the 1980s, tried to initiate large-scale sequencing using the original Sanger radioactive methods. He had three industrial partners: one to automate the sequencing reactions, another to prepare preformed gels, and a third to undertake scanning of the autoradiograms. He correctly predicted that a factory approach to sequencing would find a ready market. His project was ahead of its time and although some tens of kilobases were sequenced using his system, it failed because the right technology was not yet available.

Fluorescent primer sequencing, introduced by Lee Hood and Lloyd Smith, the invention of chain-terminating reporters by George Trainor at du Pont, and the development of sequencing machines by Applied Biosystems were essential steps in making large-scale sequencing possible. So, too, was the availability of the relatively cheap large-scale computing to handle all the data. To plagiarise Groucho Marx, it was technology and money, and computing and money, and management and money, and cash and money.

In the early days of discussions of sequence factories, as first put forward by Walter Gilbert, most people found the whole idea of a sequence sweatshop distasteful and demeaning but few people came up with alternatives. I had a very good scheme but like most of my other proposals in genomics, nobody took it seriously. I thought we should put sequencing machines into shopping malls and supermarkets and let people pay a couple of dollars a base to run them. Each day a 'bingo' sequence would be displayed above the machine. Anybody finding this in the sequence their dollars had paid for would receive a prize of $1,000. The profits from the enterprise would be used to pay the exorbitant salaries of bioinformaticians required to develop algorithms to select the sequences and to make sure that we would not be ruined by picking an *Alu* or some other highly repetitive element as the bingo sequence.

I was once asked whose genome would we first sequence. My reply was that it would be the Unknown Genome. But it occurs to me after the recent events that we need to recognise symbolically the large number of people who made the draft sequence possible. We need to have the Tomb of the Unknown Sequencer and on every anniversary of what might come to be called Armistice Monday, we should pay our respect to these unsung heroes of the Human Genome.